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Impaired Left Ventricular Contractile Function in Patients With Long-Term Mitral Regurgitation and Normal Ejection Fraction

MARK R. STARLING, MD, FACC, MARVIN M. KIRSH, MD, DANIEL G. MONTGOMERY, BS, MILTON D. GROSS, MD

Ann Arbor, Michigan

Objectives. We tested the hypotheses that left ventricular chamber elastance would detect impaired contractile function in patients with long-term mitral regurgitation and a normal ejection fraction and that these patients would have unique temporal left ventricular size and ejection fraction responses to mitral valve surgery.

Background. Although it has been suggested that left ventricular contractile function may begin deteriorating in patients with long-term mitral regurgitation whereas ejection fraction remains normal, no data exist in humans.

Methods. We studied 11 control patients and 28 patients with long-term mitral regurgitation using micromanometer-measured pressures, biplane contrast cineventriculography and radionuclide angiography under control conditions and with alterations in load during right atrial pacing to calculate left ventricular chamber elastance and myocardial stiffness.

Results. The patients with mitral regurgitation were classified into subgroups: Group I, normal contractile function; Group II, impaired contractile function (reduced E_{max}) but normal ejection fraction, and Group III, impaired contractile function (reduced E_{max}) with reduced systolic myocardial stiffness.

Twenty-two of the patients with mitral regurgitation underwent mitral valve surgery. In Group I, comparable decreases in left ventricular volume indexes ($p < 0.01$ and $p = 0.05$, respectively) were associated with no change in ejection fraction at 3 months and 1 year. In contrast, in Group II, reductions in volume indexes ($p < 0.0001$ and $p < 0.001$) were associated with a short-term decrease in ejection fraction ($p < 0.001$) that recovered at 1 year ($p < 0.01$ vs. short-term). Finally, in Group III, variable responses in volume indexes were associated with a consistent decrease in ejection fraction at 3 months and 1 year.

Conclusions. An analysis of left ventricular chamber elastance provides data to support the concepts that 1) contractile function is impaired in some patients with long-term mitral regurgitation and a normal ejection fraction, 2) impaired contractile function may not be irreversible in all of these patients, and 3) an earlier consideration of mitral valve surgery may be warranted to preserve contractile function in these patients.

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The hemodynamic course of patients with long-term, severe mitral regurgitation is characterized by progressive left ventricular dilation and dysfunction (1). Noninvasive and invasive descriptors of left ventricular size and function (2–7) have suggested that among patients with long-term mitral regurgitation, those with reduced left ventricular ejection performance at rest before mitral valve surgery have persistent left ventricular dilation and dysfunction postoperatively, because the operation is performed late in the hemodynamic course when more severe and presumably irreversible myocardial dysfunction has supervened (2–7). However, left ventricular ejection fraction frequently remains within the normal range in long-term mitral regurgitation. A normal ejection fraction may be misleading because it has been suggested (1) that left ventricular contractile function may begin a slow but progressive deterioration at this time. Although such deterioration is implicit in this disease process, no data are available to demonstrate that it does, indeed, occur in patients with long-term mitral regurgitation. Moreover, if a deterioration in left ventricular contractile function can be identified in such patients with a normal left ventricular ejection fraction, it is not known whether this observation has value for predicting the temporal response of left ventricular size and ejection fraction to mitral valve surgery.

Accordingly, we tested the hypotheses that left ventricu-

From the Division of Cardiology, Nuclear Medicine and Cardiothoracic Surgery in the Departments of Internal Medicine and Surgery, The University of Michigan and Veterans Affairs Medical Centers, Ann Arbor, Michigan. This study was supported by Grant R01-HL36450 from the National Heart, Lung, and Blood Institute and Grant M01-RR00042 from the Kughn Clinical Research Center, National Institutes of Health, Bethesda, Maryland and by the Department of Veterans Affairs, Washington, D.C. Dr. Starling is the recipient of NIH Research Career Development Award K04-HL01787 from the National Heart, Lung, and Blood Institute. This work was presented in part at the 61st and 63rd Annual Scientific Sessions of the American Heart Association, Washington, D.C., November 1988 and Dallas Texas, November 1990 and at the 39th Annual Scientific Session of the American College of Cardiology, New Orleans, Louisiana, March 1990.

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Address for correspondence: Mark R. Starling, MD, Department of Internal Medicine, Division of Cardiology, Veterans Affairs Medical Center, 2215 Fuller Road, Ann Arbor, Michigan 48105.

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lar chamber elastance, a relatively load-independent index of left ventricular contractile function, would identify a deterioration in contractile function in patients with long-term mitral regurgitation and a normal ejection fraction and that the patients in whom this observation is made would have left ventricular size and ejection fraction responses to mitral valve surgery that differed temporally from those of patients with mitral regurgitation and normal contractile function.

Methods

Patients. The study group consisted of 28 patients with long-term, severe mitral regurgitation and 11 control patients with atypical chest pain, whose clinical characteristics, hemodynamic data and left ventricular chamber elastance data were similar to those of a larger cohort of 25 patients previously described by this laboratory (8,9). The data reported previously from the larger cohort of control patients are used in this investigation only to define the normal limits for left ventricular chamber elastance. The present control group consisted of nine men and two women aged 38 to 60 years (mean ± SD 48 ± 8).

The group with long-term mitral regurgitation consisted of 27 men and 1 woman aged 36 to 72 years (mean 56 ± 11). They were drawn from a larger group of 36 consecutive patients with mitral regurgitation, who were referred for cardiac catheterization to establish the hemodynamic significance of their valvular heart disease. Eight of these 36 patients were not included in this study because of one or more of the following: concomitant mitral stenosis (n = 1) or coronary artery disease (n = 4), induction of atrial fibrillation at cardiac catheterization (n = 2), technical difficulties with data acquisition (n = 2) and patient refusal (n = 2). Of the 28 patients with long-term mitral regurgitation, 6 were in New York Heart Association clinical class I, 9 were in class II, 11 were in class III and 2 were in class IV. All patients had normal sinus rhythm and all had 4+ angiographic mitral regurgitation.

Administration of all diuretic, beta-adrenergic blocking, calcium-channel blocking and vasoactive medications was stopped 24 to 48 h before cardiac catheterization; nitrates were withdrawn 12 h before catheterization. All patients gave written informed consent on forms approved by the Human Studies Committees at the University of Michigan or Veterans Affairs Medical Centers, Ann Arbor, Michigan.

Protocol. After baseline intracardiac pressures, cardiac output and normal coronary anatomy were documented by diagnostic right and left heart catheterization, the control patients and patients with long-term mitral regurgitation entered the protocol. It consisted of the simultaneous recording of micromanometer-measured left ventricular pressures, biplane contrast cineangiography and radionuclide angiography under control conditions and during methoxamine or nitroprusside infusions to produce multiple additional left ventricular loading conditions with heart rate held constant by right atrial pacing. The methoxamine infusion was adjusted to achieve a variable increase of 20 to 50 mm Hg in left ventricular pressure, and the nitroprusside infusion was adjusted to achieve a variable decrease of 10 to 40 mm Hg in left ventricular pressure. A stable hemodynamic condition was considered present when the micromanometer-measured left ventricular systolic pressure varied by ≥10 mm Hg.

Twenty-two of the 28 patients with mitral regurgitation underwent mitral valve replacement or repair on the basis of available clinical, noninvasive and cardiac catheterization data. The decision whether to perform mitral valve surgery was not influenced by the study data. Twenty-one of these 22 patients have had a follow-up evaluation of their clinical status and left ventricular size and ejection fraction by radionuclide angiography at 3 and 12 months after mitral valve surgery. One patient developed aortic valve endocarditis and died before the 3-month follow-up evaluation.

Hemodynamics. After completion of the diagnostic cardiac catheterization, a bipolar pacing catheter was placed in the right atrial appendage to maintain a constant heart rate throughout the protocol. A micromanometer-tipped catheter (Millar Instrument) was positioned for measurement of left ventricular pressure and performance of biplane contrast cineventriculography. An Electronics for Medicine VR-12 or Micor physiologic recorder was used to obtain hemodynamic recordings at 100-mm/s paper speed. These recordings included an electrocardiographic (ECG) lead, micromanometer-measured left ventricular and aortic pressures (200-mm Hg scale) and the first derivative of left ventricular pressure (dP/dt). These were obtained simultaneously with cine frame markers during biplane contrast cineangiography. They were also recorded for 10 to 20 cardiac cycles at the beginning, middle and end of each radionuclide acquisition. An average left ventricular pressure waveform was used to match with the corresponding radionuclide left ventricular volume data.

The pressure waveforms were hand-digitized using a Calcomp 9100 inductance digitizing surface (resolution 0.02 mm) interfaced to an IBM XT beginning at the peak of the R wave of the simultaneously recorded ECG (9,10). This program yields instantaneous left ventricular pressure and dP/dt at a variable sampling frequency. Interpolation of the left ventricular pressure data was performed to guarantee isochronicity of the left ventricular pressure values with the middle of each cineangiographic frame pair and with the midpoint of each radionuclide frame.

Biplane contrast cineventriculography. Biplane contrast cineventriculography was performed in the 30° right anterior oblique and 60° left anterior oblique projections after the injection of 36 to 48 ml of Renografin-76 at 60 frames/s (16.7-ms sampling frequency). One of the first three beats after contrast injection that did not follow a ventricular ectopic beat was used for volume analysis (11). Left ventricular volumes were calculated frame by frame using a sonic digitizer (Science Accessories) mounted on a Vanguard XR-35 cine projector and interfaced to an IBM XT. The long

axes were measured in both projections from the apex to the junction of the aortic and mitral valve planes. With these long axes and the digitized silhouettes, a modified Simpson's rule algorithm was used to calculate left ventricular volumes frame by frame as previously validated in this laboratory (12).

Midwall circumferential stress (σ_θ) was used to quantitate the integrated contribution of left ventricular pressure, chamber geometry and wall thickness to myocardial fiber loading. Left ventricular end-diastolic wall thickness was determined from the digitized average dimension between the epicardial and endocardial surfaces of the left ventricular anterior free wall over the middle one third of the long axis in the 30° right anterior oblique projection (9). Left ventricular mass was calculated using the approach of Rackley et al. (13). Frame by frame estimates of left ventricular wall thickness were obtained by using the iterative approach of Hugenholtz et al (14). With the corresponding digitized left ventricular pressures, the left ventricular long axes and minor dimensions and the estimated left ventricular wall thicknesses, frame by frame midwall circumferential stresses were calculated using the equation of Mirsky (15) as:

$$\sigma_\theta = (Pb/h)(1 - h/2b - b^2/2a^2),$$

for a thick-walled ellipsoid of revolution. In this equation, P is the instantaneous left ventricular pressure, h is the estimated left ventricular wall thickness and a and b are midwall semi-major and semi-minor axes, respectively.

Radionuclide angiography. Gated equilibrium radionuclide angiograms were obtained in duplicate at each level of left ventricular load after in vivo red blood cell-labeling with 30 mCi of technetium-99m for 30-ms frames throughout the cardiac cycle for 250 cardiac cycles. During the midportion of each radionuclide acquisition, a 2-ml blood sample was drawn. Blood samples were later counted for 2 min, and the time delay between acquisition and counting of the blood samples was recorded. At the end of the protocol, measurements were made for each patient to determine the distance from the gamma scintillation camera in the left anterior oblique projection to the center of the left ventricle for attenuation correction. The attenuation-corrected radionuclide volumes were then calculated frame by frame using background-subtracted, hand-drawn region of interest left ventricular count data, decay-corrected blood sample counts and attenuation correction as previously validated in this laboratory (16,17).

Radionuclide left ventricular ejection fraction (EF) was calculated as:

$$EF = [(EDV - ESV)/EDV] \times 100,$$

where EDV represents maximal left ventricular volume and ESV represents minimal left ventricular volume. Right ventricular (RV) stroke counts were obtained using a modification of the method described by Maddahi et al. (18), which we have used to calculate right ventricular volumes to compare with those obtained from biplane contrast cineventriculography (19) and to calculate right ventricular volumes and EF in patients with right ventricular infarction (20,21). We calculated left ventricular (LV) regurgitant index (RI) as:

$$RI = (LV\ EDC - LV\ ESC)\ (RV\ EDC - RV\ ESC),$$

where EDC and ESC represent maximal and minimal left ventricular and right ventricular counts, respectively.

Assessment of left ventricular contractile function. We used two different approaches to assess contractile function: left ventricular chamber elastance and systolic myocardial stiffness. First, the corresponding micromanometer-measured left ventricular pressures and radionuclide left ventricular volumes for each loading condition were plotted to generate multiple (n = 3 to 8, mean 5) pressure-volume loops in each patient. Then, isochronal instantaneous pressure-volume data points from each loading condition were subjected to linear regression analysis to obtain the maximal slope (E_{max}) and the extrapolated volume-axis intercept (V_0). Because this approach is not conventional, we also subjected the maximal pressure/volume ratio from each pressure-volume loop to linear regression analysis to obtain a slope (E_{es}) and V_0 value. Both E_{max} and E_{es} were used as relatively load-independent indexes of left ventricular contractile function (22–25).

In patients with left ventricular volume overload, heart size should be considered to determine whether E_{max} or E_{es} is appropriate for chamber size. Because several approaches have been proposed (8,26–30), but none has been universally accepted, we used two different methods. In one approach, we used the method of Berko et al. (27), which has been further evaluated and applied in our laboratory (8), together with another method of multiplying E_{max} or E_{es} by left ventricular end-diastolic volume or mass (29). We did not multiply by V_0, as suggested by Suga et al. (30), because many patients, particularly those with left ventricular volume overload, had negative V_0 values.

In the second approach we used the systolic myocardial stiffness concept to correct midwall circumferential stress-shortening relations for variations in preload to identify those patients with long-term mitral regurgitation who had impaired left ventricular contractile function with more severe and presumably, irreversible myocardial dysfunction. Because this concept incorporates the variables of left ventricular size, shape, wall thickness, and mass in addition to left ventricular pressure into the calculation of myocardial fiber load and relates these to the extent of shortening, it is apparent that systolic myocardial stiffness should provide somewhat different information about left ventricular contractile function from that provided by E_{max} or E_{es}. Thus, by using both approaches, it was hypothesized that we would separate mild and potentially reversible from more severe and presumably irreversible contractile impairment in these patients with long-term mitral regurgitation.

Adequate biplane contrast cineventriculograms were obtained for this purpose in 26 of 28 patients with mitral

regurgitation. In this analysis (29,31), the instantaneous midwall circumferential stress (σ_θ) or the instantaneous stress difference (σ) was used. The stress difference was computed as $\sigma_\theta - \sigma_{ra}$, where $\sigma_{ra} = -1.36$ (P/2) and P is instantaneous left ventricular pressure. The units of stress are in g/cm^2 and the units of P are mm Hg. As initial studies (31) demonstrated the load independence of systolic myocardial stiffness, the end-systolic stress-strain relations were given by:

$$\sigma es = K_m \cdot maxEav \cdot (e_\theta)es,$$

where natural strain (e_θ) at end-systole is equal to log (bes/b_0), bes is the instantaneous midwall minor diameter at end-systole, b_0 is the midwall minor diameter at zero stress and the constant k_m is equal to (2/3) (2 + b^2/a^2).

To approximate zero stress volume (V_0) and zero stress diameter (b_0), a curve-fitting routine was applied to the circumferential stress and stress difference-volume (diameter) data from peak stress to the first minimal volume (diameter) point, such that V_0 (b_0) were obtained from the equation: σ_θ or $\sigma = A - B \cdot V\ (b)^{-\alpha} = 0$, where A, B and α are curve-fitting variables. The relation between afterload (σ_θ or σ) and shortening at a comparable "normal" preload (σ_{ed}) can then be obtained from the complex equation:

$$(k_m \cdot \Gamma \cdot maxEav) \log [(100 - EF)V_{ed}/V_0 \cdot 100] = G \cdot \sigma_\theta/(G - 0.68),$$

where the constants Γ and G were obtained from the left ventricular minor diameter versus volume and σ_θ or σ/P versus volume plots from peak stress to stress at the first minimal volume point in each patient (29,31). Thus, this approach converts the linear stress-strain relation into the stress-volume plane where left ventricular ejection fraction can be calculated for any σ_θ from peak stress to the first minimal volume point after correction for the variable effects of left ventricular preload (V_{ed} at a common σ_{ed}) on left ventricular ejection fraction.

To estimate the end-diastolic volume (V_{ed}) at a comparable normal diastolic stress, the σ_θ-volume data points from minimal pressure to end-diastolic pressure were smoothed, and then V_{ed} was obtained directly as the maximal left ventricular diastolic circumferential stress, which was comparable in all 11 control patients. In our control patients, this value for σ_θ was 36 g/cm^2, which is comparable to that previously reported by Mirsky et al. (29).

End-systole was defined in this study as maxEav, which occurred one to five frame pairs before the first minimal volume point in these patients with long-term mitral regurgitation. This observation is consistent with our prior observation in similar patients in whom E_{max} was used as a marker of end-systole (32). Thus, it would appear that whether E_{max}, E_{es} or maxEav is used to define end-systole, the time of occurrence of this systolic event is similar.

Surgical technique. Twenty-two patients underwent mitral valve surgery. All patients were cooled to a systemic temperature of 28°C, and myocardial preservation was achieved by using cardioplegic solution instilled into the aortic root or retrograde through the coronary sinus to maintain myocardial temperature between 10° and 15°C. Supplemental topical hypothermia was used as needed. Although all patients with long-term mitral regurgitation were considered candidates for mitral valve repair, only seven patients underwent repair. The other 15 patients had mitral valve replacement; the integrity of the submitral apparatus was maintained (33) in 7 (of these 15 patients) but was not maintained in 8. The average pump time in these patients was 123 ± 42 min, and the average cross-clamp time was 70 ± 35 min.

Statistical analysis. Unless otherwise indicated, all data are presented as the mean value ± 1 SD. Comparisons of hemodynamic variables were made between the control patients and the patients with long-term mitral regurgitation using nonpaired *t* tests. Differences between the ability of various indexes to detect abnormal left ventricular systolic function in the patients with mitral regurgitation were identified using McNemar's test (34).

The patients with mitral regurgitation were subgrouped according to their preoperative values for E_{max} and systolic myocardial stiffness. Then, between-group comparisons and comparisons with the control patients were performed by using an analysis of variance. When a significant F statistic was obtained, Dunnett *t* tests were used to identify differences.

Within-group comparisons of the preoperative and postoperative data were performed using analysis of variance with repeated measures. In addition, to compare data in subgroups of patients with mitral regurgitation with different preoperative left ventricular size and ejection fraction values, changes in data at each postoperative time point from the preoperative values were calculated and then compared between the patient subgroups. Nonpaired *t* tests were again used to identify differences between Groups I and II because Group III had too few patients for statistical comparisons. A probability value ≤ 0.05 was used to determine statistical significance.

Results

Baseline hemodynamic data. The average baseline hemodynamic data in the 11 control patients and 28 patients with long-term mitral regurgitation are shown in Table 1. The average heart rate, left ventricular systolic and end-diastolic pressures, left ventricular ejection fraction, σ_θ values at end-diastole and end-systole and V_0 values did not differ between the control group and the patients with mitral regurgitation. However, in the latter patients, values for left ventricular end-diastolic volume index, end-systolic volume index and mass were greater ($p < 0.0001$) and E_{max} was lower ($p < 0.0001$) than the corresponding values in the control group. The radionuclide left ventricular regurgitant index averaged 2.72 ± 1.41 in the patients with mitral regurgitation.

Table 1. Baseline Hemodynamic Data in Control Patients and in Patients With Long-Term Mitral Regurgitation (MR)

	n	HR (beats/min)	LVP (mm Hg)	LVEDP (mm Hg)	EDVI (ml/m²)	ESVI (ml/m²)	EF (%)	RI	MASS (g)	$\sigma_\theta$ed (g/cm²)	$\sigma_\theta$es (g/cm²)	E_{max} (mm Hg/ml)	V_0 (ml)
Control	11	78 ± 10	132 ± 8	13 ± 3	53 ± 18	20 ± 8	62 ± 12	—	172 ± 60	43 ± 23	189 ± 82	5.28 ± 1.49	18 ± 13
MR	28	85 ± 7	125 ± 18	16 ± 8	139 ± 35*	61 ± 26*	57 ± 11	2.72 ± 1.41	245 ± 52*	60 ± 32	206 ± 77	1.68 ± 1.18*	16 ± 61
Group I	11	83 ± 12	134 ± 20	14 ± 6	113 ± 24	45 ± 14	60 ± 10	2.50 ± 0.99	235 ± 51	60 ± 36	206 ± 78	2.91 ± 0.86	48 ± 39
Group II	13	84 ± 18	116 ± 10†	15 ± 6	149 ± 30†	60 ± 20‡	60 ± 8	2.90 ± 1.79	245 ± 68	61 ± 31	184 ± 55	0.96 ± 0.43§	7 ± 63
Group III	4	91 ± 25	131 ± 19	23 ± 12	181 ± 20	107 ± 15	41 ± 6	2.82 ± 1.31	371 ± 60	75 ± 23	269 ± 108	0.64 ± 0.36	−46 ± 61

*p < 0.0001 versus control; †p < 0.01, ‡p < 0.05, §p < 0.0001 versus Group I. $\sigma_\theta$ed = circumferential stress at end-diastole; $\sigma_\theta$es = circumferential stress at end-systole; E_{max} = left ventricular chamber elastance; EDV = left ventricular end-diastolic volume; EF = left ventricular ejection fraction; ESV = left ventricular end-systolic volume; HR = heart rate; LVP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; RI = left ventricular regurgitant index; V_0 = extrapolated unstressed volume for E_{max}.

Left ventricular systolic function. In the patients with long-term mitral regurgitation assessment of left ventricular systolic function as abnormal depended on the index used. The E_{max} and E_{es} values in these patients were significantly, and similarly, different from values in the control patients (8) (Fig. 1): Average E_{max} was 1.75 ± 1.16 mm Hg/ml ($p < 0.0001$ vs. control), and averaged E_{es} was 1.28 ± 1.14 mm Hg/ml ($p < 0.0001$ vs. control). The correlation between the individual E_{max} and E_{es} values was $r = 0.85$ ($p < 0.0001$) even though average E_{max} and E_{es} values differed ($p < 0.0001$). Using 2 SD below the mean E_{max} and E_{es} as the lower limits of normal (1.98 and 0.99 mm Hg/ml, respectively), both E_{max} and E_{es} provided highly concordant determinations of whether left ventricular contractile function was normal or impaired in the patients with mitral regurgitation ($k = 0.63$, $p < 0.01$).

The normal limits (±2.5 SD) for systolic myocardial stiffness were generated in the 11 control patients and are shown in Figure 2. These values reflect the preload-corrected shortening (ejection fraction [EF_c]) at operational afterload (σ_θ) at end-systole. The individual systolic myocardial stiffness values for the 26 patients with mitral regurgitation are plotted against these normal limits. Only 4 (16%) of these 26 patients had an abnormal systolic myocardial stiffness value.

The proportion of patients with long-term mitral regurgitation who were defined as having abnormal left ventricular systolic function was greater if the abnormality was defined by E_{max} or E_{es} (17 of 28 patients, 61%) than if it was defined by a radionuclide left ventricular ejection fraction of ≤45% (3 of 28 patients, 10%, $p < 0.01$ vs. E_{max} or E_{es}) or depressed myocardial stiffness (4 [16%] of 26 patients, $p < 0.05$ vs. E_{max} or E_{es}). These observations imply that left ventricular contractile function may be impaired even when left ventricular ejection fraction is normal and such impairment is not necessarily due to more severe and possibly irreversible myocardial dysfunction.

Figure 1. Left ventricular radionuclide maximal slope (Emax) and (Ees) values for the 25 control patients previously used to define the lower limits for this relation (8) are compared with values for the patients with long-term mitral regurgitation (MR). Note the comparable number of patients with mitral regurgitation and an abnormal Emax or Ees. *p < 0.0001 compared with the normal value. The large circles and bars indicate mean value ± SD.

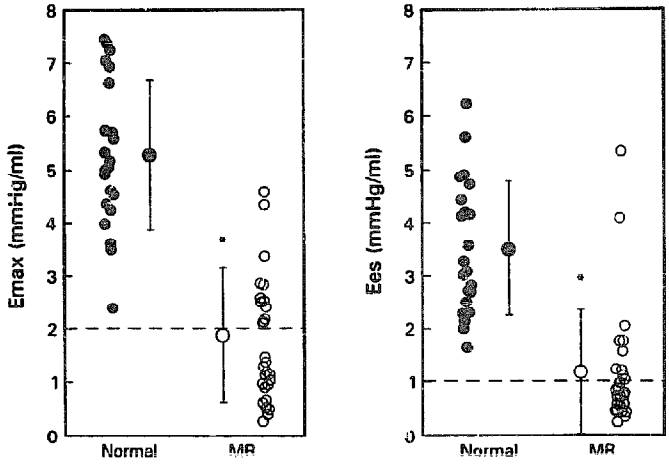
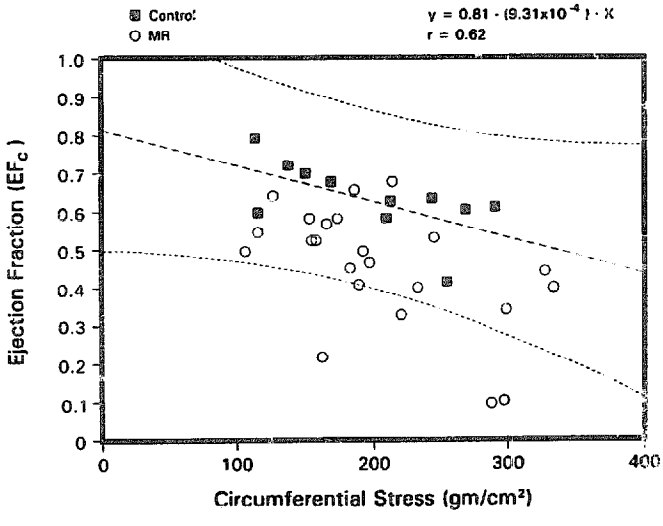


Figure 2. Relation between cineangiographic left ventricular end-systolic midwall circumferential stress (abscissa) and ejection fraction (ordinate), obtained using the systolic myocardial stiffness concept, for the control patients and patients with long-term mitral regurgitation (MR). The normal limits (long dashes) (±2.5 SD, short dashes) for the control patients are shown for this relation. Only 4 (16%) of the 26 patients with long-term mitral regurgitation had an abnormal relation. EF_c = corrected ejection fraction.



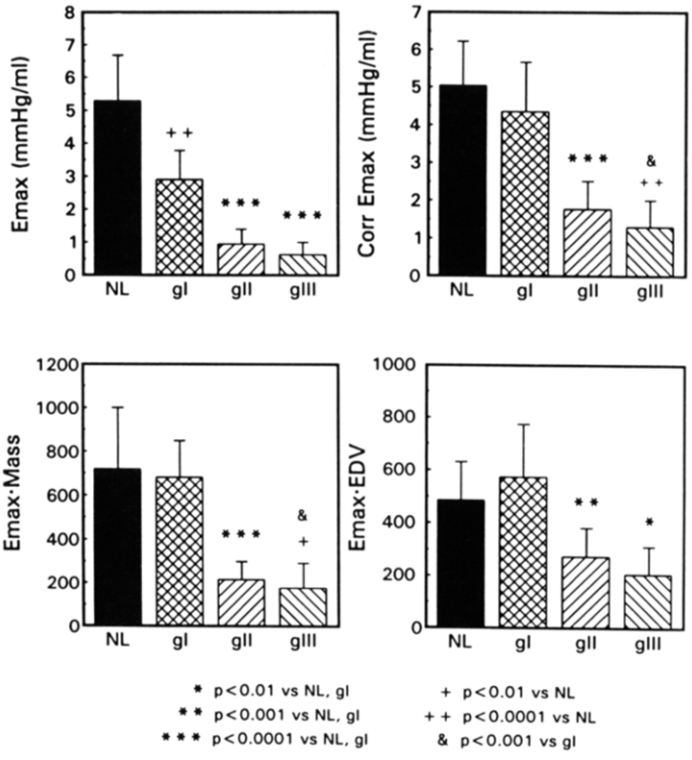


Figure 3. The radionuclide maximal slope (Emax) **(upper left panel)**, end-diastolic volume (EDV)–standardized Emax **(upper right panel)**, EDV multiplied Emax **(lower left panel)** and left ventricular mass–multiplied Emax **(lower right panel)** values are compared between the 11 control patients and the Group I, II and III patients (gI, gII, gIII) with long-term mitral regurgitation. Significant differences are shown. Group I patients had a comparable heart size–corrected Emax value compared with that of the control patients, irrespective of the method of standardization. This was not true for Groups II and III. NL = normal (control) patients.

Because E_{max} and E_{es} provided the same data on left ventricular contractile function in these patients, only E_{max} was used in subsequent analyses. Accordingly, because no patient had both abnormal myocardial stiffness and a normal E_{max}, three subgroups of patients with mitral regurgitation were characterized: Group I, normal left ventricular contractile function; Group II, impaired contractile function, and Group III, impaired contractile function with more severe and presumably irreversible myocardial dysfunction.

To determine whether the reduction in E_{max} in these patients with long-term mitral regurgitation was related to heart size, we used several approaches to correct E_{max} (8,27–29). As shown in Figure 3, the average corrected E_{max} in Group I did not differ from that in the control group, irrespective of our approach to considering the influence of left ventricular size. In contrast, despite an increase in E_{max} from 0.96 ± 0.43 to 1.78 ± 0.74 mm Hg/ml in Group II and from 0.64 ± 0.36 to 1.31 ± 0.68 mm Hg/ml in Group III (Fig. 3, upper right), these corrected E_{max} values continued to differ from values in the control group and Group I ($p < 0.001$ to $p < 0.0001$). Similar observations were made when E_{max} was multiplied by left ventricular end-diastolic volume or mass (Fig. 3, lower panels). Thus, once the influence of heart size was removed from the determination of E_{max}, left ventricular contractile function in Group I was no different from that in the control group, but it was variably impaired in Groups II and III.

Clinical response to mitral valve surgery. In the 21 patients with mitral regurgitation who underwent mitral valve surgery and postoperative clinical and functional evaluation, functional class improved from 2.5 ± 0.9 to 1.6 ± 0.7 ($p < 0.001$). After mitral valve surgery, 10 patients were asymptomatic, whereas 9 were in functional class II and only two were in class III. No patient was in class IV. This clinical improvement persisted at 1 year.

Left ventricular size and ejection fraction response to mitral valve surgery. Left ventricular end-diastolic and end-systolic volume indexes, ejection fraction and regurgitant index responses to mitral valve surgery were examined in the 21 patients with long-term mitral regurgitation who survived to have a postoperative radionuclide angiogram at 3 and 12 months. In this group, left ventricular end-diastolic volume index decreased from 139 ± 35 to 96 ± 49 ml/m^2 ($p < 0.001$) at 3 months and remained reduced at 1 year (107 ± 23 ml/m^2, $p < 0.001$). End-systolic volume index decreased from 61 ± 26 to 51 ± 40 ml/m^2 at 3 months, but individual responses were variable and this index decreased further to 45 ± 20 ml/m^2 at 1 year ($p < 0.01$). In contrast, left ventricular ejection fraction averaged 57 ± 11% preoperatively, decreased to 50 ± 13% at 3 months ($p < 0.01$) but returned to 57 ± 14% ($p < 0.01$ vs. 3 months) at 1 year. The left ventricular regurgitant index decreased from 2.72 ± 1.41 to 1.40 ± 0.73 ($p < 0.0001$) at 3 months and to 1.31 ± 0.61 ($p < 0.001$) at 1 year.

When left ventricular size and ejection fraction responses to mitral valve surgery were examined for each hemodynamic subgroup of patients with long-term mitral regurgitation, different temporal responses were evident (Fig. 4). In Group I patients, there were comparable reductions in left ventricular end-diastolic and end-systolic volume indexes ($p < 0.01$ and $p = 0.05$, respectively) with no change in ejection fraction. In contrast, in Group II patients, a distinctly different pattern emerged. Left ventricular end-diastolic volume index was reduced from 146 ± 30 before operation to 84 ± 17 ml/m^2 at 3 months ($p < 0.0001$) and remained reduced at 1 year (105 ± 21 ml/m^2, $p < 0.001$) despite the notable increase between 3 months and 1 year ($p < 0.001$). Similarly, left ventricular end-systolic volume index decreased from 60 ± 20 to 45 ± 14 ml/m^2 at 3 months ($p < 0.001$) and remained reduced at 1 year (43 ± 11 ml/m^2, $p < 0.01$). Because of these volume changes, left ventricular ejection fraction decreased from 60 ± 8 to 47 ± 7% at 3 months ($p < 0.001$) but increased at 1 year to 59 ± 5% ($p < 0.01$ vs. value at 3 months, p = NS vs. preoperative value). There were relatively few Group III patients, who had severe and probably irreversible contractile impairment. In general, left ventricular end-diastolic and end-systolic volume indexes varied after valve surgery, with a resultant

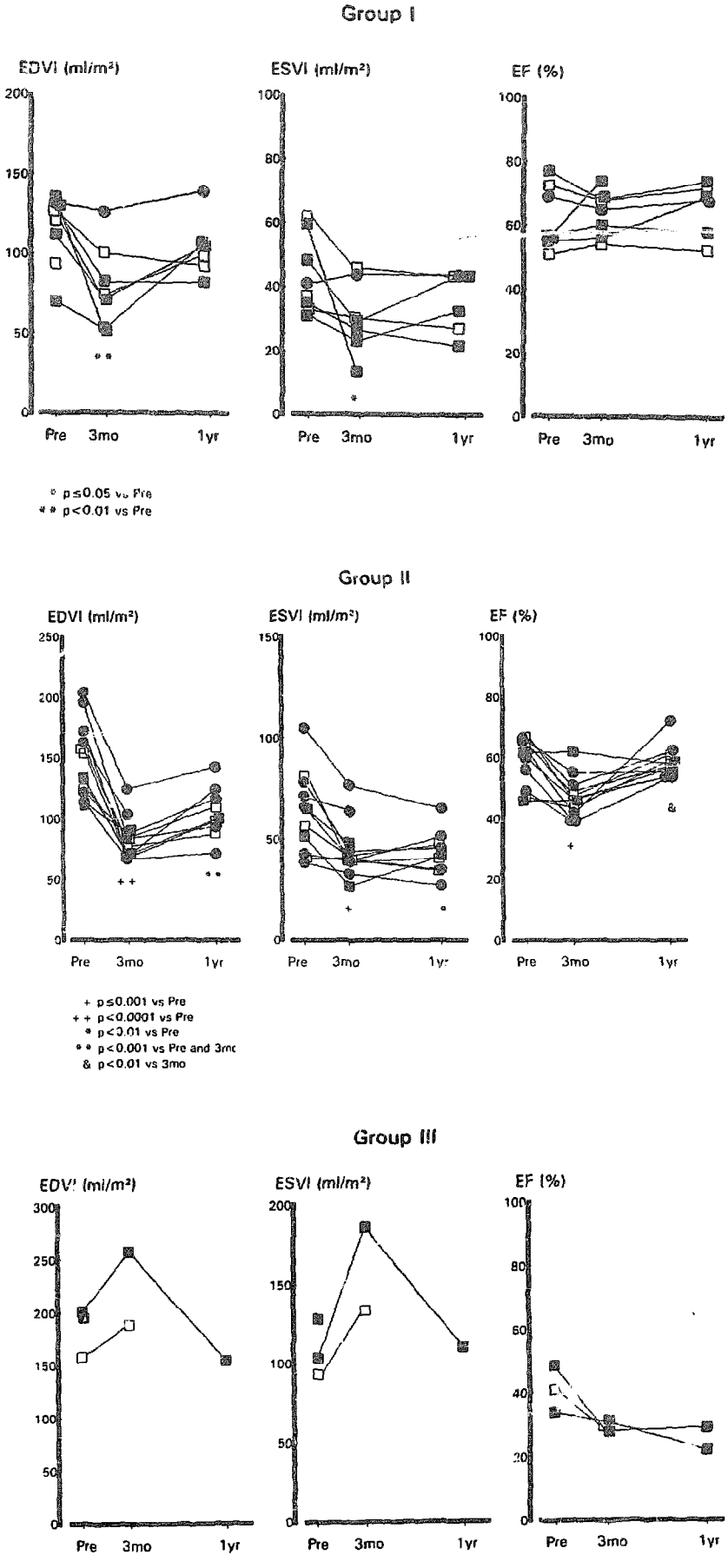


Figure 4. The preoperative to postoperative individual responses in radionuclide left ventricular end-diastolic volume index (EDVI), end-systolic volume index (ESVI) and ejection fraction (EF) in Group I, II and III patients with long-term mitral regurgitation. Group I comprises patients with long-term mitral regurgitation who had normal preoperative (pre) left ventricular contractile function; Group II, those with impaired left ventricular contractile function, and Group III, those with impaired left ventricular contractile function that is more severe with presumably irreversible myocardial dysfunction. The individual values for each patient in the three subgroups are encoded for the type of mitral valve surgery performed. The **solid circles** represent those who had mitral valve repair; the **solid squares**, those with mitral valve replacement and submitral continuity preserved, and the **open squares**, those with a mitral valve replacement without submitral continuity. Significant changes are noted.

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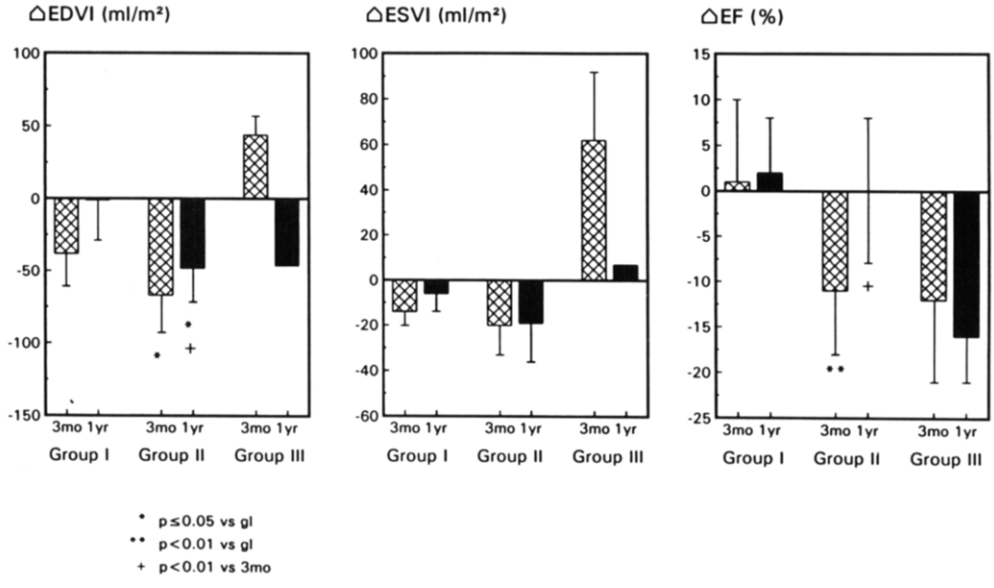

Figure 5. The data shown in Figure 4 are illustrated in a different format. The changes in radionuclide left ventricular end-diastolic volume indexes (EDVI), end-systolic volume indexes (ESVI) and ejection fractions (EF) are shown as the absolute change from their corresponding preoperative values. This eliminates the preoperative differences in these variables between subgroups so that comparisons between subgroups can be made. Notably, there was a greater decrease in left ventricular end-diastolic volume index at 3 months than at 1 year in Group II, which resulted in a greater reduction in left ventricular ejection fraction at 3 months and a subsequent increase in left ventricular ejection fraction at 1 year after mitral valve surgery in comparison with Group I (gI). The left ventricular size and ejection fraction responses to mitral valve surgery in Group III were poor. Significant differences are noted.

reduction in left ventricular ejection fraction that persisted from 3 months to 1 year.

To further illustrate the differences in the left ventricular volume and ejection fraction responses to mitral valve surgery in the three subgroups of patients with long-term mitral regurgitation, the changes in left ventricular volumes and ejection fraction from preoperative values were calculated (Fig. 5). Left ventricular end-diastolic volume index changes differed between Group I and II patients at 3 months and at 1 year ($p < 0.05$ for both). Consequently, although absolute values for left ventricular end-diastolic volume index differed between Groups I and II preoperatively, they did not differ early or late postoperatively. The changes in left ventricular end-systolic volume index did not differ between Groups I and II early or late postoperatively. The average left ventricular end-systolic volume index in these two groups did differ early postoperatively ($p < 0.05$) but not at 1 year because this index increased in Group I but remained reduced in Group II. Because of these volume responses, left ventricular ejection fraction decreased in Group II but not in Group I ($p < 0.01$) at 3 months, so that the left ventricular ejection fraction in Group II was less than that in Group I at 3 months ($p < 0.01$). However, there was no difference in the average left ventricular ejection fraction values at 1 year between these two groups because of a significant increase in left ventricular ejection fraction in Group II between 3 months and 1 year ($p < 0.01$). In contrast, left ventricular ejection fraction decreased in Group III at both 3 months and 1 year.

Differentiation of patients with mitral regurgitation by left ventricular volume indexes. The average preoperative hemodynamic values in the three subgroups of patients with long-term mitral regurgitation are shown in Table 1. The average heart rate, left ventricular end-diastolic pressure, regurgitant index, and σ_θ value at end-diastole and end-systole did not differ among the three subgroups. Left ventricular systolic pressure was lower in Group II than in Group I ($p < 0.01$).

The radionuclide left ventricular end-diastolic and end-systolic volume index values averaged 53 ± 18 and 20 ± 8 ml/m^2, respectively, in the control group and demonstrated a progressive increase from Group I to III. In contrast, left ventricular ejection fraction averaged 62 ± 12% in the control group and was similar in both Group I and Group II patients (60 ± 10 and 60 ± 8%, respectively). It decreased to 41 ± 6% only in Group III. These data suggest that it might be possible to differentiate the hemodynamic subgroups of patients with long-term mitral regurgitation with normal (Group I) or impaired (Group II) left ventricular contractile function by using the individual radionuclide or cineangiographic values for left ventricular end-diastolic and end-systolic volume indexes because they were different in these patients. However, individual values for end-diastolic and end-systolic volume indexes overlapped substantially between Group I and II patients. Despite differences in the mean values for these two indexes, patients with normal (Group I) or impaired (Group II) left ventricular contractile function could not be separated at optimal cut points of

125 ml/m^2 for left ventricular end-diastolic volume index (χ = 1.36, p = NS) or 50 ml/m^2 for end-systolic volume index (χ = 2.71, p = NS). Thus, left ventricular volume indexes are not useful discriminators between patients with mitral regurgitation characterized by normal or impaired left ventricular contractile function.

Discussion

The natural history of long-term mitral regurgitation is characterized by a progressive increase in left ventricular size and reduction in left ventricular ejection fraction (1). The initial phase of this hemodynamic course is characterized by compensatory, eccentric left ventricular hypertrophy to maintain normal end-diastolic and end-systolic stresses (35). This phase is presumably followed by a period in which impaired left ventricular contractile function insidiously develops. This latter phase may be obscured by a normal left ventricular ejection fraction, which occurs because of the favorable left ventricular loading conditions presented by the left atrium preserving ejection performance (32). With the late development of more severe and presumably irreversible myocardial dysfunction, the long-term outcome in patients with mitral regurgitation is poor. Indeed, commonly used invasive and noninvasive indexes of left ventricular size and ejection performance identify patients who do poorly after mitral valve surgery (2–7). These patients have persistent left ventricular dilation and dysfunction, probably resulting from the onset of irreversible myocardial dysfunction before mitral valve surgery (6). However, a hemodynamic profile that identifies patients with long-term mitral regurgitation at a time in their hemodynamic course when mitral valve surgery might be performed with the expectation of preserving left ventricular ejection performance has remained elusive.

The data in the present study demonstrate that impaired left ventricular contractile function occurs in patients with long-term mitral regurgitation and normal left ventricular ejection fraction. This was evident because left ventricular chamber elastance identified a greater proportion of patients with long-term mitral regurgitation who had abnormal left ventricular systolic function than were identified by ejection fraction. Moreover, impaired left ventricular contractile function begins to develop well before more severe and presumably irreversible myocardial dysfunction can be documented. Consequently, three subgroups of patients with long-term mitral regurgitation, who had temporally different left ventricular size and ejection fraction responses to mitral valve surgery, were characterized. Group I patients had normal left ventricular contractile function whereas Group III represents those patients who probably have structural changes of myocardial architecture (36) and more severe and probably irreversible myocardial dysfunction. Group II patients had less impaired left ventricular contractile function evidenced by a reduced E_{max}, but left ventricular ejection fraction was maintained at a normal end-systolic stress and consequently, systolic myocardial stiffness was maintained. These differences were inherent to the study methods used and were therefore useful in this investigation for separating from the large group of patients with mitral regurgitation who have left ventricular contractile impairment, those with more severe myocardial dysfunction and an unsatisfactory functional outcome after mitral valve surgery.

Group I patients had compensated left ventricular volume overload, manifested by an increase in left ventricular volumes that was matched with adequate eccentric left ventricular hypertrophy (36). Left ventricular contractile function was not impaired in Group I as the heart size–corrected E_{max} did not differ from that in the control groups, irrespective of the method used to correct for heart size (8, 26–29). This finding was further exemplified by the responses of left ventricular size and ejection fraction to mitral valve surgery. Group I patients had modest, comparable reductions in left ventricular end-diastolic and end-systolic volume indexes and had no significant change in left ventricular ejection fraction after mitral valve surgery. This group could adapt successfully to the immediate alterations in hemodynamic load resulting from surgical correction of long-term mitral regurgitation without impairment of left ventricular ejection performance, probably because of normal left ventricular contractile function.

In contrast, in Group II, impaired left ventricular contractile function, manifested by a reduction in E_{max}, had developed. This observation was further evidenced by the left ventricular size and ejection fraction responses to mitral valve surgery. Postoperatively, Group II patients had a greater reduction in left ventricular end-diastolic volume index than in end-systolic volume index, commensurate with the removal of the left ventricular volume overload. These changes resulted in a reduced left ventricular ejection fraction at 3 months. These left ventricular size and ejection fraction responses differed from those in Group I. Nevertheless, in Group II, left ventricular ejection fraction was restored to normal at 1 year, a recovery that was unique to this subgroup of patients. Thus, these data suggest that earlier consideration of mitral valve surgery for long-term mitral regurgitation, when left ventricular contractile function may be only mildly impaired and potentially reversible, rather than more severe and probably irreversibly impaired, will result in preservation of left ventricular ejection fraction at 1 year.

These data explain why some patients with long-term mitral regurgitation and a normal preoperative left ventricular ejection fraction have little change in left ventricular ejection fraction after mitral valve surgery, whereas others have a substantial reduction in ejection fraction, sometimes to well below the normal range. The data in the present study suggest that this transient reduction of left ventricular ejection fraction in some patients with long-term mitral regurgitation is due to mild but reversible impairment of left ventricular contractile function. This is supported by four recent observations in animal models of left ventricular volume overload and in humans. First, in a porcine model of

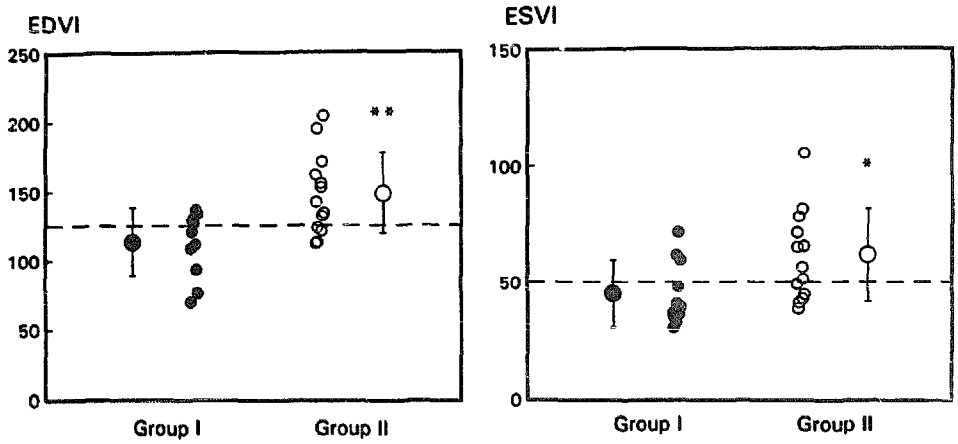

Figure 6. The individual left ventricular end-diastolic volume index (left panel) and end-systolic volume index (right panel) values for patients with long-term mitral regurgitation in Groups I and II. The individual overlap is apparent and substantial. Despite optimal cut points of 125 and 50 ml/m^2, these cut points did not discriminate between these subgroups, suggesting that the E_{max} values obtained in these patients with long-term mitral regurgitation are not a function of left ventricular size.

* $p<0.05$ vs Group I
** $p<0.01$ vs Group I

chronic left ventricular volume overload produced by an aorta-caval fistula, Hammond et al. (37) demonstrated the down-regulation of left ventricular beta-receptors and uncoupling of G-stimulating proteins without evidence of myocardial inflammation or fibrosis. These data suggest that in the setting of chronic left ventricular volume overload, an increase in plasma norepinephrine can cause myocardial biochemical changes that may lead to impaired left ventricular contractile function in the absence of primary myocardial damage. More important, these biochemical changes may be reversible. This possibility is supported by recent experimental (38) and clinical (39) observations. Nakano et al. (38) in animals with long-term mitral regurgitation noted impaired left ventricular contractile function in the setting of a normal left ventricular ejection fraction after 3 months of experimental mitral regurgitation. After surgical correction of the regurgitation, left ventricular contractile function improved despite a short-term decrease in ejection fraction. Starling (39) also noted improved left ventricular contractile function in patients with long-term mitral regurgitation, who had left ventricular contractile function assessed before and 1 year after mitral valve surgery. In further support of this concept, preliminary data from Spinale et al. (40) demonstrated, in an animal model of chronic mitral regurgitation, that treatment with a beta-blocking agent can limit the down-regulation of left ventricular beta-receptors and preserve left ventricular contractile function. Therefore, these observations in animals and patients with long-term mitral regurgitation suggest that left ventricular contractile function may be impaired despite a normal left ventricular ejection fraction and that at least mildly impaired contractile function may be reversible.

Finally, it is important to appreciate that the determination of whether left ventricular contractile function was normal or impaired was not a function of heart size. It is well known that E_{max} or E_{es} is related to heart size (8,26–30). Although the influence of heart size on E_{max} may be small, a correction for this potential confounding influence was performed. As noted in Table 1, only left ventricular end-diastolic and end-systolic volume indexes differed between Groups I and II after the subgrouping based on E_{max}. In contrast, Figure 6 shows that substantial individual overlap occurs for these volume indexes, so that they do not provide discriminatory cut points for separating these two subgroups. These data suggest that E_{max} is not reduced because of heart size; rather, they suggest that, irrespective of heart size, left ventricular contractile function is impaired in group II whereas E_{max} is normal in Group I.

There is, however, a time when left ventricular contractile impairment becomes irreversible. Our data confirm the observations of other investigators that after the development of more severe and apparently irreversible myocardial dysfunction (Group III), the response to mitral valve surgery is poor. Several previous studies (2–7,41) have reported that patients with mitral regurgitation and severe left ventricular dilation and a preoperative reduction in left ventricular ejection performance have persistent left ventricular dilation and dysfunction postoperatively presumably because of irreversible contractile impairment. The presence of abnormal systolic myocardial stiffness in our Group III and their response to mitral valve surgery are consistent with these data (2–7,41). Consequently, our findings further emphasize the importance of performing mitral valve surgery in patients with long-term mitral regurgitation and a normal left ventricular ejection fraction (Group II) when left ventricular contractile impairment is less severe and potentially reversible.

Limitations of the study. There are three potential limitations to our investigation. First, left ventricular loading conditions were altered pharmacologically to generate E_{max} and E_{es} values with reflexes left intact. As in previous studies from this laboratory (9,10,28,32,42,43), right atrial pacing was performed to eliminate the influence of alter-

ations in heart rate on these relations (44). Moreover, we (10,45) have previously reported that the modest alterations in left ventricular loading conditions performed in this study do not alter isovolumetric indexes of contractility or relaxation. These data are consistent with similar observations reported from intact animals (46,47), which suggest that greater alterations in left ventricular load are necessary to produce reflex sympathetic effects on left ventricular contractility.

Second, we assumed that E_{max} and E_{es} were linear. However, E_{max} and E_{es} may not be linear under all circumstances (48–50). This occurs principally at the extremes of left ventricular load (50). However, Little et al. (51) have shown that within the operational range of left ventricular pressures and volumes, the relation can be assumed to be linear. Consequently, we considered it reasonable to assume linearity in our patients. This may explain why the important data obtained from the time-varying elastance concept in our patients resided with E_{max} not with V_0 because the latter may be significantly affected by curvilinearity.

Finally, we did not control for the type of mitral valve surgery performed. Mitral valve repair was performed in seven patients and mitral valve replacement, in 15 patients. In some patients, mitral valve repair may preserve or at least cause less depression in left ventricular ejection fraction than does mitral valve replacement. Recent animal studies have demonstrated the importance of the subvalvular apparatus for maintaining left ventricular contractile function (52). In this study, mitral valve repair and replacement were distributed between the three subgroups of patients with long-term mitral regurgitation, and no apparent difference was identified within each subgroup in the individual responses of left ventricular size and ejection fraction to mitral valve surgery (Fig. 4), probably owing to the relatively small number of patients with each type of operation in each subgroup. There are two further important considerations in this regard: 1) despite a substantial body of clinical data supporting preservation of left ventricular ejection fraction with mitral valve repair compared with replacement, no clinical study has so extensively assessed left ventricular systolic function in so homogeneous a population of mitral regurgitation patients as the present study, and 2) although it was not our intention to compare the effects of the type of mitral valve surgery on left ventricular ejection fraction, our data should not be used to imply that left ventricular contractile function may not be preserved by mitral valve repair. In a study with more patients with mitral regurgitation, a difference might have been noted, particularly in Groups II and III.

In conclusion, analysis of left ventricular contractile function using the time-varying elastance concept provides data that identify a unique subgroup of patients with long-term mitral regurgitation and a normal left ventricular ejection fraction, in whom impaired left ventricular contractile function exists. The response of these patients to mitral valve surgery was temporally unique and characterized by an early reduction and a late (1 year) recovery of left ventricular ejection fraction. Accordingly, these data imply that impaired left ventricular contractile function may not be irreversible in all patients with long-term mitral regurgitation, and they support the concept that an earlier consideration of mitral valve surgery may be warranted to preserve left ventricular contractile function in some of these patients with a normal left ventricular ejection fraction.

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